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Intravenous Administration of VX in Man

by

Kazuo K. Kimura, M.D.

Bernard P. McNamara, Ph.D.

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July 1960

ARMY CHEMICAL CENTER, MD.

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U. S. ARMY
Chemical Corps Research and Development Command
CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
Army Chemical Center, Maryland

FOREWORD

The work presented in this report was authorized under Project 4C08-02-022, Medical Aspects of CW (U), Task 4C08-02-022-03, Clinical Investigation and Treatment of CW Casualties (U). The study was carried out under the Medical Research Directorate Research Task Plan No. 3049 with the recommendations of the VX Committee for Utilization in Man. The work was started in February 1958 and completed in August 1959.

Acknowledgments

Two of the authors (K. K. Kimura, M.D. and B. P. McNamara, Ph.D.) wish to acknowledge the fortitude of Van M. Sim, M.D. in volunteering for the initial three pilot tests which laid the foundation for all subsequent human studies with VX. Both of the authors realize that they are reporting experiments which required not only the volunteers but the entire staff, both clinical and laboratory, to make this report possible. Any error or any shortcoming in the interpretation of data rests with the reporters and the credit must extend to all those who participated in these tests.

Clinical Research Division: (b) (6)

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DIGEST

Intravenous studies on VX in man were conducted to obtain precise dose-effect relationships using the route of administration where the exact amount of agent given could be controlled without the influence of absorption problems. These results formed the basis of subsequent percutaneous studies of VX in man.

1. Intravenous VX studies were carried out on 7 volunteer subjects who received either single 30-second injections or slow intravenous infusions.

2. Dose employed ranged from 0.04 to 2.12 μg/kg.

3. At 1 μg/kg symptoms may occur and cholinesterase levels will fall to 45% to 50% of normal.

4. Total of 2.12 μg/kg given over 5-1/2 hours seems to be the maximum tolerable dose intravenously without using atropine, oximes, and/or artificial resuscitation.

5. Red blood cell and whole blood cholinesterase determinations by both the modified Michel method and the electrolytic method seem to correlate well, particularly at higher doses.

6. There are advantages in an investigation such as this to determine the cholinesterase activity in whole blood as well as in plasma and red blood cells. The method used for whole blood yields a reliable quantitative answer in 10 to 15 minutes. This gives invaluable support to the medical officer responsible for the well being of the volunteer.

7. Red blood cell cholinesterase depression to 35% to 50% of normal after intravenous VX returns to 80% to 90% of normal within 14 days.

INTRAVENOUS ADMINISTRATION OF VX IN MAN

I. INTRODUCTION.

Extensive toxicity studies in several animal species have indicated that the intravenous LD50 for VX range from 4 to 20 μg/kg of body weight.[1] It was the opinion of the authors that the initial intravenous dose for man would safely be 1/100 of the intravenous LD50 (or 0.04 μg/kg) for the most sensitive animal. One of the authors (Dr. Sim) volunteered to be the subject for the dose-effect study with intravenously administered VX. Following the information obtained from the pilot study, it was planned that a group of 6 volunteers from the enlisted volunteer program would be utilized for the purpose of obtaining (a) information on the dose-effect relationship of VX to cholinesterase depression and (b) relationship of intravenous VX to clinical signs and symptoms. The purpose of the entire task plan was to form a firm basis for subsequent extensive percutaneous studies of VX in man.

II. METHODS.

To ensure maximum safety and full utilization of the initial pilot study, the following steps and studies were planned:

1. Complete physical examination of the volunteer subject including all vital signs, electrocardiogram, chest X-ray, hemogram, blood chemistries, cholinesterase determinations, and urinalyses were made during the control periods preceding the test day. Cholinesterase determinations were made simultaneously by the modified Michel method of Stubbs and Fales[2] and the electrolytic method of Trurnit and Vocci[3] as modified by Vocci.[4]

2. Special tests included electroencephalograms, airway-resistance measurements, galvanic-skin-resistance measurements, and spirometer studies.

III. DOSAGES.

It was apparent that the doses selected had to be carefully chosen as initial trials gave indications of the dose-effect relationship.

A. Part I.

Initially, 0.04 μg/kg was planned for the intravenous injection over a 30-second period. With the negligible effect produced by this dose, the next dose was 0.08 μg/kg for the same subject on the same day making the total dose 0.12 μg/kg.

B. Part II.

Eighteen months later* the same subject was given twice the dose or 0.225 μg/kg intravenously over a 30-second period.

C. Part III.

Two hours after the initial rapid injection a continuous intravenous drip of VX was begun. The blood cholinesterase levels were determined frequently by the rapid electrolytic method.

D. Part IV.

Six enlisted volunteers under the Clinical Research Division Volunteer Program were selected to receive 1 μg/kg of VX intravenously over different infusion periods as shown in table 1.

TABLE 1

INFUSION TIME FOR INTRAVENOUS VX

No.	Subject	Infusion time
1	(b) (6)	4
2		4
3		4
4		4
5		2.5
6		1.75

To preclude any clinical difficulty, a resuscitation team was available at the bedside to administer atropine, oximes, oxygen, artificial resuscitation, and tracheotomy if indicated. All doses and VX dilutions were checked, and double checked by the two authors directing the study (Dr. Kimura and Dr. McNamara).

* This delay period was necessitated awaiting official permission from the Department of the Army to conduct further studies on VX.

IV. RESULTS.

A. Part I.

The total of 4.4 μg (0.04 μg/kg) was given intravenously over a 30-second injection period at 1000 hours on 27 February 1958 while the subject was under 5-hour fast.

No particularly noticeable result was obtained except front and retrobulbar headaches starting 45 minutes after the VX was injected. There were no consistent significant depression of the cholinesterase levels. It was noted by the observers that the subject seemed quite irritable and reported feeling tired.

Exactly 3.5 hours after the first injection of VX, 8.8 μg (0.08 μg/kg) were given intravenously over a 30-second period. The following results shown in table 2, were obtained.

TABLE 2

TIME OF ONSET OF EFFECTS OF INTRAVENOUS INJECTIONS OF VX

Time after injection	Results
min	
15	2-Fold increase in airway resistance, 25% to 30% decrease in respiratory rate, and 15% drop in the pulse rate
20	Onset of frontal and retrobulbar headaches
30-45	Increase in minute volume from 15 to 32 liters
45	Peak effect of the agent with conscious respiration, feeling sweaty (although there were no increase in skin resistance), lightheadedness, and abdominal cramps.

Although the subject appeared irritable and talked less clearly during the peak effect, pupil size did not change and he did not have any obvious

respiratory difficulty. There were no muscular twitching or fasciculations, salivation, nausea, or vomiting. Electrocardiograms, cholinesterase determinations, and all blood chemistries (pH, CO_2, O_2, sugar, lactic acid) were within normal limits.

B. Part II.

On 21 August 1959 the same subject (Dr. Sim) was given a rapid 30-second intravenous injection of 0.225-μg/kg or 27.5 μg total dose which resulted in the first definite evidence of cholinesterase depression. The systolic blood pressure dropped from the control of 145/92 to 134/90 lasting for over an hour. Within 10 to 15 minutes after injection the respiratory minute volume rose from the baseline of 10 to 27 liters; it dropped to control levels within an hour. Pupillary dilatation was not remarkable, but dilated from the control of 2 mm in diameter to 3 mm for approximately 45 minutes with the onset of mydriasis at 20 minutes after injection. The airway resistance did not change significantly. The cholinesterase level determinations by the modified Michel method showed the fall in cholinesterase from the control 0.88 to 0.70 to 0.73 ΔpH units/hour within 10 to 15 minutes after injection. Expressed in per cent of baseline figures, the electrolytic method showed the fall in red cell cholinesterase from 100% to 63% level in 15 minutes. The subject complained of feeling hot and again experienced the frontal and retrobulbar headaches which seemed to last during the entire phase of cholinesterase depression for approximately a 30-minute period with the onset appearing about 30 minutes after the injection.

The graphic representation of the above events is presented in figure 1 on the left-hand portion covering the period from 0 to 120 minutes elapsed time.

C. Part III.

Two hours after the injection of 0.225 μg/kg of VX the subject (Dr. Sim) was given slow continuous infusion of VX at the rate of 1 μg/minute until the cholinesterase levels definitely fell below 50% of normal. The infusion was continued until the red blood cell and whole blood cholinesterase levels had dropped to approximately 15% of normal. The graphic representation of the course of events is given in figure 1 for the elapsed time period from 120 minutes to 480 minutes. The minute volume increased considerably at the peak of VX effect, and also to a less degree when the rate of infusion was temporarily increased. Airway-resistance measurements did not seem to change appreciably. The pupils dilated for approximately 1 hour from 2-mm diameter to 3-mm size at the peak effect of the agent.

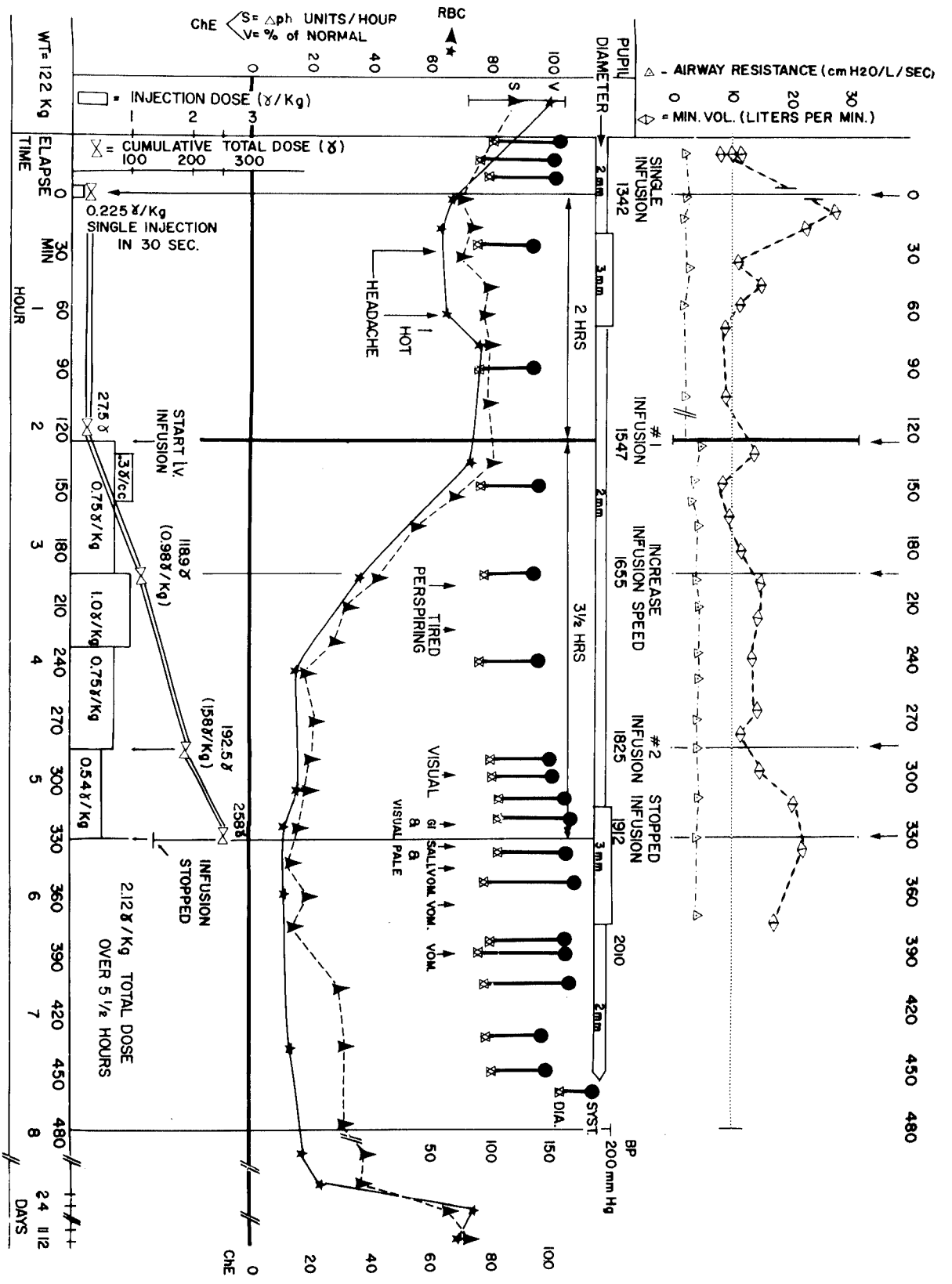

FIGURE 1

INTRAVENOUS VX IN MAN

There was a slight increase in blood pressure. During the later period of the experiment there was a definite increase in perspiration, salivation, pale appearance, nausea, and vomiting. The subject in the earlier phase complained of feeling tired and had visual distortion in which the colleagues appeared to be somewhat taller and very thin. The post-experiment cholinesterase levels gradually increased but did not commence to come back to the 60% to 80% level until the third to fourth days.

At one point, approximately 3-1/2 hours after the onset of the continuous infusion, the subject suddenly became pale, stopped talking, and appeared out of contact with the responsible medical officer (Dr. Kimura). At this point the decision was made to discontinue the infusion of VX. A few minutes after this the subject announced that he felt spinny and started to salivate and was not able to keep the air from leaking around his mouth while having his minute volume measurements taken. Vomiting started at this point. Approximately 20 minutes after infusion was terminated, the subject became irrational and started to thrash around and wanted to have the various venous indwelling catheters removed. This confusional and irrational period lasted about 15 minutes. One of the venous indwelling catheters was kept in place in event the subject required resuscitation measures such as intravenous atropine or the oximes.

About an hour after the termination of the infusion and about 30 minutes after his confusional period, the subject started to feel better and started to communicate with the members of the experimental team. The subject vomited several times and his color did not improve until 1 hour and 40 minutes after termination of the infusion. The subject was observed overnight in the Volunteer Program Facility.

Comparative results of the cholinesterase-determination methods for red blood cell, plasma, and whole blood are presented in figure 2. From these experiments, it was estimated that the intravenous ChE50 would be about 1 μg/kg. To obtain further information this dose was given to six enlisted volunteers. The results of these tests are presented in figures 3 and 4. The maximum cholinesterase depression from the baseline control level of 100% was approximately in the range of 34% to 45% of normal. Four subjects receiving a 4-hour infusion of 1 μg/kg had the maximum drop in cholinesterase at the end of the infusion period. Those who received the same dose over a shorter infusion period showed an earlier and steeper rate of fall in the blood cholinesterase levels, but the maximum drop was approximately the same as that obtained for the 4-hour infusion period. Figure 4 shows the gradual return of the red blood cell cholinesterase levels for the six volunteer subjects.

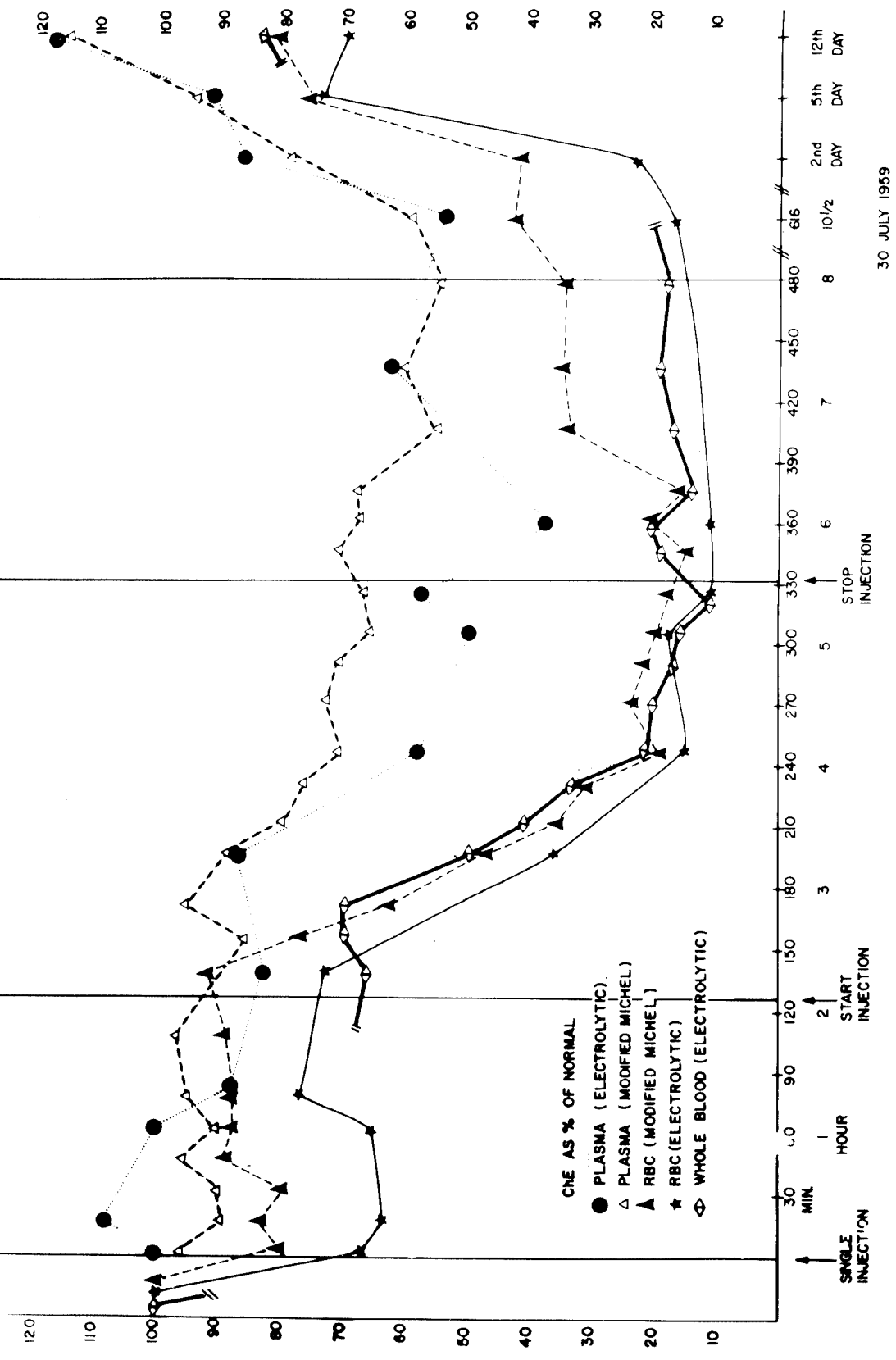

FIGURE 2

CHOLINESTERASE LEVELS IN MAN

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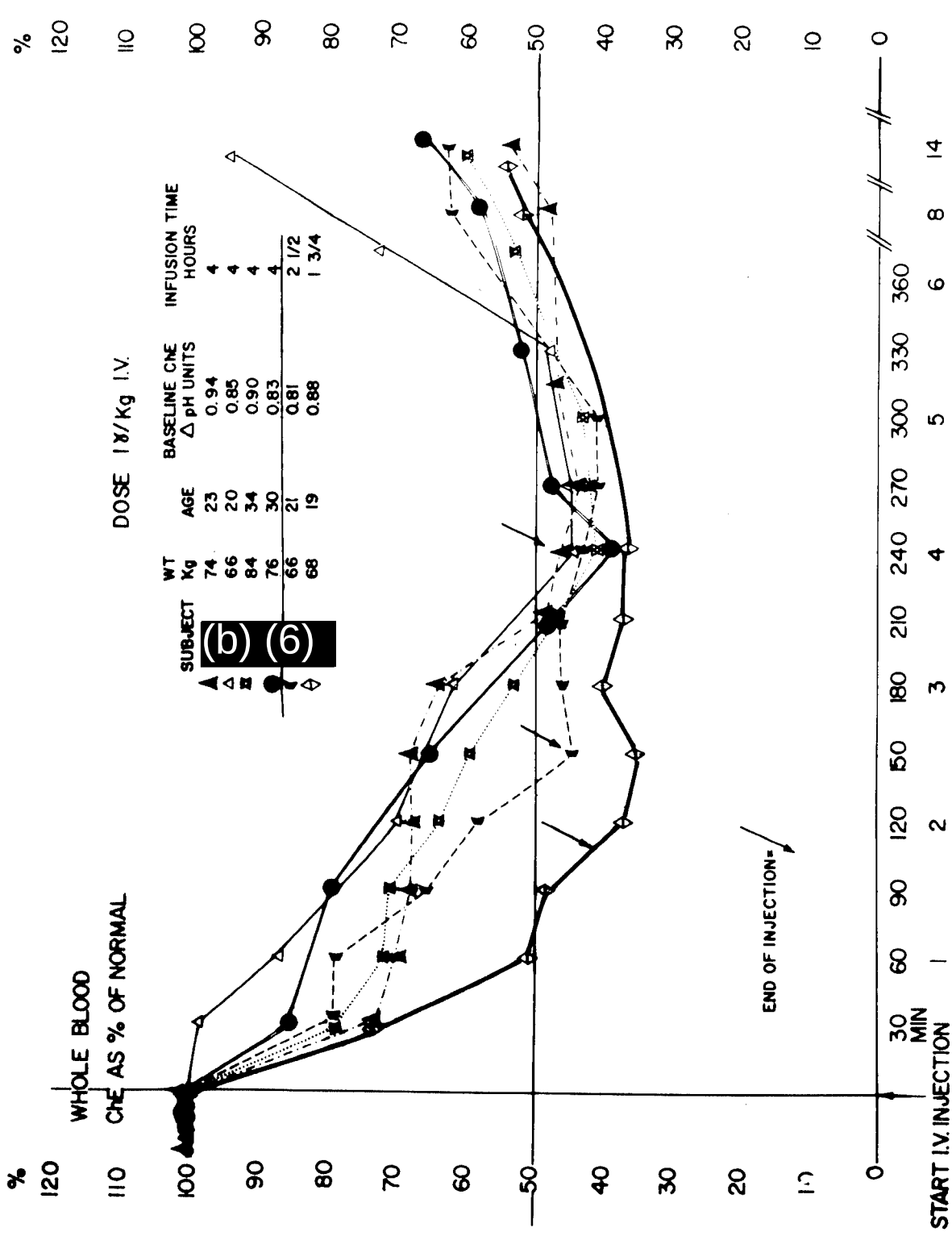

FIGURE 3

CHOLINESTERASE LEVELS

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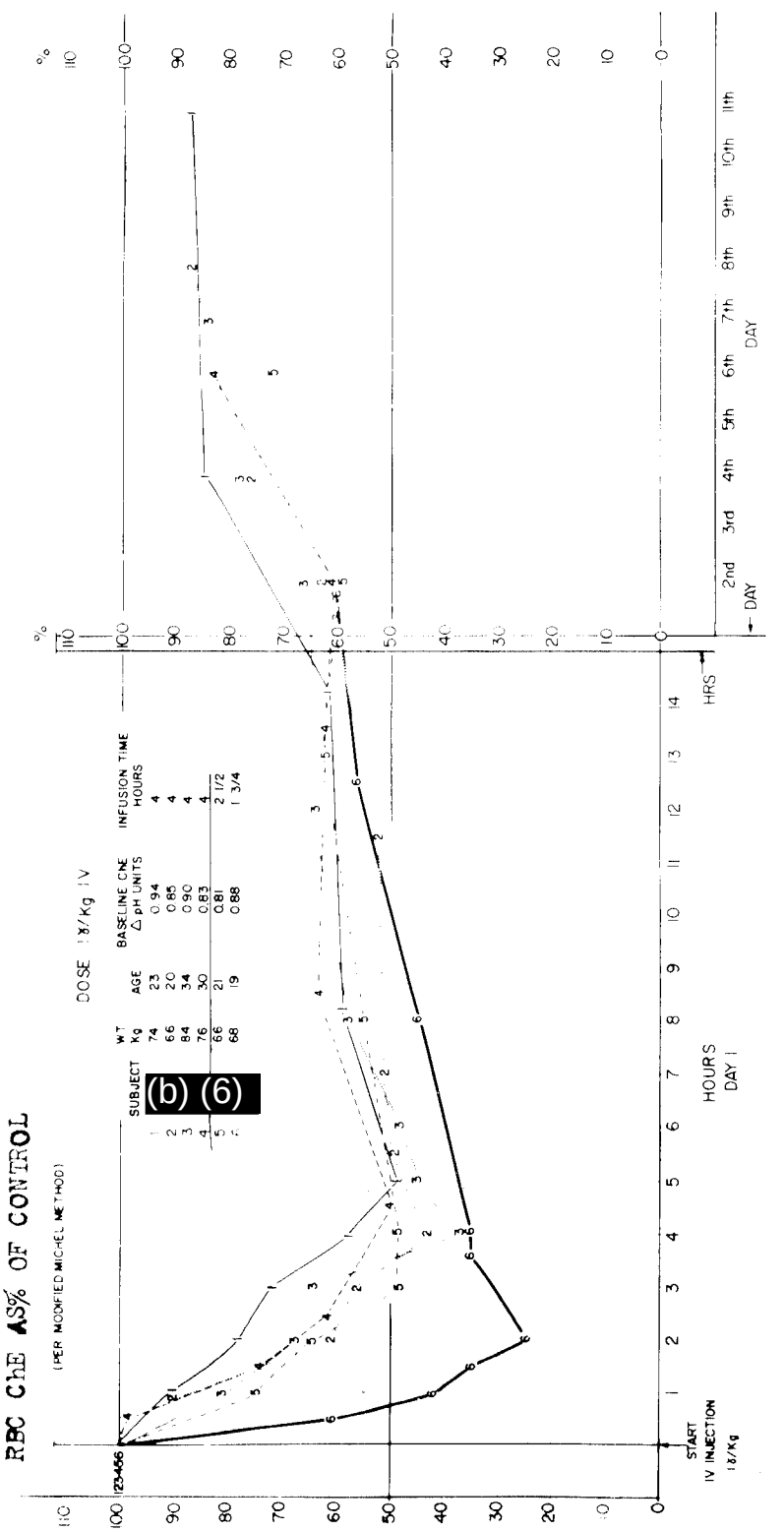

FIGURE 4

CHOLINESTERASE LEVELS IN MAN

III. DISCUSSION.

These intravenous VX studies in man were necessary steps for obtaining dose-effect relationships with special reference to the cholinesterase levels and signs and symptoms of poisoning.

The small initial doses of 0.04 and 0.08 μg/kg produced only trace effects while the minimum effective dose for cholinesterase depression was in the neighborhood of 0.225 μg/kg intravenously. When this dose and an additional 1.9 μg/kg were given by infusion over a 3-1/2-hour period giving a total of 2.12 μg/kg over a 5-1/2-hour period, the subject definitely showed symptoms of toxicity, period of irrationality, and definite depression of red blood cell, whole blood, and plasma cholinesterase levels. Certainly if the 2.12-μg/kg dose had been given as a single bolus over a 30-second period, there may have been considerable difficulty in handling the subject. There seems to be a sharp differentiation between 1 μg/kg producing about 40% to 50% depression of cholinesterase and 2 μg/kg, which could be expected to produce toxicity requiring resuscitative measures, such as atropine, oximes, and respiratory assist.

The six enlisted volunteers who received enough VX to produce more than 50% fall in cholinesterase levels certainly had minimal, if any, signs and symptoms. The only subject who did complain of headache and appeared uncomfortable was the heaviest and the oldest of the group weighing 84 kg and being 34 years of age (figure 3).

Figure 2 showing the comparisons of the two cholinesterase-determination methods with whole blood, red blood cell, and plasma strengthened confidence in the methods for following cholinesterase levels in the volunteer subject receiving VX. Although there seems to be considerable scatter of cholinesterase values down to approximately the 75% level, from this point down to 10% to 15% there appears to be good correlation between whole blood and red cell cholinesterase values. This is apparent in figure 2. The plasma cholinesterase values do not seem to show the precise correlation that the red blood cell or whole blood values show. However, in general, both the electrolytic and the modified Michel method indicate the trend of the plasma cholinesterase levels during the course of the experiment.

These results seem to indicate that the dose of 1 μg/kg given intravenously over a 30-second period would produce at least 50% fall in circulating cholinesterase. The results obtained with the higher dose infusion allowed observation of valuable signs and symptoms which will aid in the evaluation of VX given percutaneously[5] in man where the entire skin acts as a barrier to diffusion or penetration of the agent into the blood stream.

IV. SUMMARY.

1. Intravenous VX studies were carried out on 7 volunteer subjects who received either single 30-second injections or slow intravenous infusions.

2. Dose employed ranged from 0.04 to 2.12 μg/kg.

3. At 1 μg/kg symptoms may occur and cholinesterase levels will fall to 45% to 50% of normal.

4. Total of 2.12 μg/kg given over 5-1/2 hours seems to be the maximum tolerable dose intravenously without using atropine, oximes, and/or artificial resuscitation.

5. Red blood cell and whole blood cholinesterase determinations by both the modified Michel method and the electrolytic method seem to correlate well, particularly at higher doses.

6. There are advantages in an investigation such as this to determine the cholinesterase activity in whole blood as well as in plasma and red blood cells. The method used for whole blood yields a reliable quantitative answer in 10 to 15 minutes. This gives invaluable support to the medical officer responsible for the well being of the volunteer.

7. Red blood cell cholinesterase depression to 35% to 50% of normal after intravenous VX returns to 80% to 90% of normal within 14 days.

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2. Intravenous Administration of VX to Man
3. Dose-Effect Relationship of VX, intravenously injected, in man

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